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## **Sleep-wake disturbances 3 years after traumatic brain injury**

Kempf, J ; Werth, E ; Kaiser, P R ; Bassetti, C L ; Baumann, C R

**Abstract:** BACKGROUND: 6 months after traumatic brain injury (TBI), almost three out of four patients suffer from sleep-wake disturbances (SWD) such as post-traumatic hypersomnia (increased sleep need of 2 h compared with before injury), excessive daytime sleepiness (EDS), fatigue and insomnia. The long-term course of post-traumatic SWD, however, is unknown. OBJECTIVES: To assess the prevalence and characteristics of post-traumatic SWD 3 years after trauma. DESIGN: Prospective longitudinal clinical study in 51 consecutive TBI patients (43 males, eight females, mean age 40±16 years). MAIN OUTCOME MEASURES: EDS (as assessed by the Epworth sleepiness scale), fatigue (fatigue severity scale), post-traumatic hypersomnia (sleep length per 24 h), insomnia, depression and anxiety. RESULTS: Post-traumatic SWD were found in 34 patients (67%): post-traumatic hypersomnia in 14 (27%), EDS in six (12%), fatigue in 18 patients (35%) and insomnia in five patients (10%). SWD were not associated with severity or localisation of, or time interval since, TBI. Insomnia was linked to depressive symptoms. CONCLUSIONS: This prospective study shows that 3 years after TBI, two out of three patients suffer from residual SWD, particularly fatigue and post-traumatic hypersomnia. In 45% of TBI patients, SWD appear directly related to the trauma itself.

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# Sleep—wake disturbances 3 years after traumatic brain injury

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## ABSTRACT

**Background** 6 months after traumatic brain injury (TBI), almost three out of four patients suffer from sleep—wake disturbances (SWD) such as post-traumatic hypersomnia (increased sleep need of  $\geq 2$  h compared with before injury), excessive daytime sleepiness (EDS), fatigue and insomnia. The long-term course of post-traumatic SWD, however, is unknown.

**Objectives** To assess the prevalence and characteristics of post-traumatic SWD 3 years after trauma.

**Design** Prospective longitudinal clinical study in 51 consecutive TBI patients (43 males, eight females, mean age  $40 \pm 16$  years).

**Main outcome measures** EDS (as assessed by the Epworth sleepiness scale), fatigue (fatigue severity scale), post-traumatic hypersomnia (sleep length per 24 h), insomnia, depression and anxiety.

**Results** Post-traumatic SWD were found in 34 patients (67%): post-traumatic hypersomnia in 14 (27%), EDS in six (12%), fatigue in 18 patients (35%) and insomnia in five patients (10%). SWD were not associated with severity or localisation of, or time interval since, TBI. Insomnia was linked to depressive symptoms.

**Conclusions** This prospective study shows that 3 years after TBI, two out of three patients suffer from residual SWD, particularly fatigue and post-traumatic hypersomnia. In 45% of TBI patients, SWD appear directly related to the trauma itself.

## INTRODUCTION

Sleep—wake disturbances (SWD) are common after traumatic brain injury (TBI), significantly impact quality of life and interact with post-traumatic psychiatric disturbances such as depression and anxiety symptoms.<sup>1–3</sup> In the first prospective study examining sleep—wake disturbances following TBI, we found de novo SWD 6 months after trauma in 72% of 65 consecutive TBI patients.<sup>2</sup> The most prevalent SWD were excessive daytime sleepiness (EDS) and/or fatigue (in 55%), and an increased sleep need per 24 h (in 22%). Insomnia, on the other hand, was surprisingly uncommon (5%). We found no associations between post-traumatic SWD and severity or localisation of TBI, general clinical outcome or demographic characteristics such as age and gender.

Knowledge about the long-term outcome of post-traumatic SWD, however, is sparse. It is not known whether symptoms persist or improve during a longer course after TBI. To the best of our knowledge, only a few studies have examined the long-term course of post-traumatic SWD.<sup>4–6</sup> In 19 non-consecutive children and adolescents, Kaufman

and colleagues performed sleep studies 3 years after mild TBI and compared results with a control population.<sup>4</sup> They found higher total sleep times on actigraphy studies, which may indicate hypersomnia. In a recent prospective study in 87 non-consecutive patients with heterogeneous intervals (ranging from 3 months to more than 3 years) between TBI and examinations, Castriotta and colleagues found no association between the latency since TBI and the characteristics of post-traumatic SWD.<sup>5</sup> A prospective longitudinal study examined the development of fatigue during a 2-year course following TBI.<sup>6</sup> The authors observed an improvement only in the first year after TBI, and a correlation between fatigue and cognitive as well as motor symptoms.

With this study, we aimed for the first time at prospectively describing the long-time course of SWD in consecutive TBI patients. For this purpose, we extended the follow-up in our TBI study population to 3 years after TBI.<sup>2</sup> To better distinguish the interaction with psychiatric comorbidities since TBI, we also assessed depression and anxiety symptoms.

## METHODS

### Subjects

We extended the follow-up period in the same 65 consecutive TBI patients who have been systematically studied in our first report on post-traumatic SWD 6 months after TBI (mean age at trauma:  $39 \pm 16$  years, 53 men).<sup>2</sup> Briefly, all patients had an acute first-ever TBI and did not suffer from sleep—wake disturbances, psychiatric or neurological disorders prior to TBI. Patients were admitted to our hospital between July 2003 and December 2005 immediately after the injury. TBI severity was defined according to the Glasgow Coma Scale (GCS), and clinical outcome was determined by the Glasgow Outcome Scale (GOS). To assess clinical outcome, post-traumatic SWD and psychiatric disturbances, we contacted all patients 3 years after trauma, performed structured phone interviews and applied standardised questionnaires including validated scales.

### Structured phone interview

The phone interview consisted of a structured set of questions about sleep—wake behaviour since TBI, particularly about changes since the first study 6 months after TBI. The interview comprised questions on sleep quality including assessment of problems to fall asleep or sleep through, sleep duration per 24 h during weekdays and weekends,

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daytime vigilance including fatigue and EDS. The presence of parasomnias, restless legs syndrome, sleep apnoea symptoms, narcolepsy or circadian sleep–wake disturbances was explored. We also included questions on treatment of SWD, and on the interference of SWD with performance levels and quality of life. The last part of the interview consisted of questions about other residual symptoms since TBI, including headache, pain, vertigo, cognitive disturbances, depressive symptoms and changes in general behaviour. Furthermore, we assessed current medication and the ability to work, that is whether patients returned to work, full- or part time. All interviews were carried out by the first author.

### Questionnaires

After completion of phone interviews, we mailed a detailed questionnaire to each patient which is standardised in our clinic to assess sleep–wake disturbances and which includes validated scales such as the Epworth Sleepiness Scale (cut-off: 10 points),<sup>7</sup> the Sleep Apnoea Scale of the Sleep Disorders questionnaire (cut-off: 32 for women, 36 for men),<sup>8</sup> the Ullanlinna Narcolepsy Scale (cut-off: 14),<sup>9</sup> the Swiss Narcolepsy Scale (cut-off: 0)<sup>10</sup> and the Fatigue Severity Scale (cut-off: 4).<sup>11</sup> The same scales have been used in the first study at 6 months after TBI. Furthermore, to assess depression and anxiety symptoms, we applied the Hospital anxiety and depression score (HADS),<sup>12</sup> as well as the Beck Depression Inventory (BDI).<sup>13</sup>

### Definition of post-traumatic SWD

EDS was defined in the presence of Epworth sleepiness scale scores  $\geq 10$ . Fatigue was diagnosed in those patients who scored  $\geq 4.0$  on the fatigue severity scale. Post-traumatic hypersomnia was diagnosed in patients who reported an increased sleep need of at least 2 h compared with pre-TBI conditions. Insomnia was diagnosed according to the International Classification of Sleep Disorders (ICSD-2): mandatory criteria were chronic inability to fall asleep (sleep latency above 40 min) or remain sleeping despite a good occasion for sleeping; and further symptoms as for example fatigue, sleepiness, depression, anxiety or cognitive problems.<sup>14</sup> Behaviourally induced insufficient sleep syndrome was diagnosed in patients who reported EDS and a difference in sleep time between weekdays and weekends/holidays of  $\geq 2$  h.

### Statistical analyses

Statistical analyses were performed by correlation analyses, Student *t* tests for parametric variables, Mann–Whitney *U* tests for non-parametric data and one-way ANOVA to test for differences among multiple independent groups (SPSS 18.0). Changes for repeated dichotomous measures were assessed with the non-parametric McNemar test.

## RESULTS

### Patients

Three years after TBI, 51 patients (43 men, mean age  $40 \pm 16$  years, range 18–72, representing 78% of the first study consisting of 65 patients) gave oral and written consent to participate in this follow-up study. Fourteen patients were lost to follow-up (nine patients could no longer be traced, and five patients refused to participate). The distribution of TBI severity was similar to the first study 6 months after trauma: TBI was mild in 21 (42%), moderate in 11 (22%) and severe in 19 (38%) patients. Good recovery (GOS 5) was found in 24 (48%), moderate disability (GOS 4) in 24 (48%) and severe disability (GOS 3) in three (6%) patients (mean GOS  $4.4 \pm 0.6$ ).

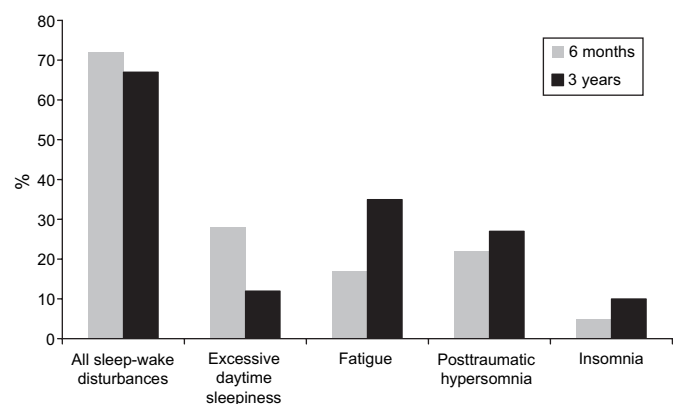
### General course

During structured phone interviews, fifteen subjects (29%) reported cognitive problems including memory and/or concentration impairment since TBI (6 months after TBI: 48%). Headache was reported by 12 subjects (24%, formerly 23%). Nine patients (18%) judged themselves to suffer from depressive symptoms (12% at 6 months after TBI), and five patients (10%) reported a change in their personality, mostly aggressive traits. Three patients were treated with antiepileptic drugs (levetiracetam, *n*=2, carbamazepine, *n*=1), and one patient took zolpidem on a regular basis to treat problems to fall asleep or sleep through. No other patient took drugs to improve sleep or wakefulness, and no patient was treated for sleep apnoea. Twenty-three patients returned to work in a full-time position, 17 worked part time, eight did not return to work, and three patients were retired. Based on the questionnaires, depression was diagnosed in nine patients (18%) and anxiety disorder in two patients (4%). BDI results correlated significantly with depression items of the HADS ( $p < 0.001$ ,  $r = 0.84$ ). Depression and anxiety parameters were not associated with TBI characteristics such as severity and localisation.

### Sleep habits, post-traumatic hypersomnia and insomnia

Figure 1 offers an overview on sleep–wake disturbances 6 months and 3 years after TBI. Thirty-five (69%) subjects judged their sleep to be deep, and 11 (22%) estimated their sleep to be superficial. Nine patients (18%) reported an overall subjective improvement of their sleep and SWD, and six patients (12%) felt their sleep problems to be deteriorated. Circadian sleep–wake disturbances or parasomnia disorders were not reported.

The mean sleep time per day during weekdays ( $8.2 \pm 1.7$  h) was similar to the findings 6 months after TBI ( $8.0 \pm 1.5$  h). The mean sleep extension during holidays or weekends ( $8.8 \pm 1.5$  h) was less than 1 h. Sleep times were not associated with TBI characteristics, TBI outcome or presence of depression or anxiety symptoms. Sleep times above 10 h during weekdays were reported by seven patients (14%). Post-traumatic hypersomnia was present in 14 patients (27%; 6 months after TBI: 22%), independently of TBI severity, localisation, outcome, psychiatric symptoms (two patients were diagnosed as having depression), gender or age. The difference in sleep time between weekdays and weekends was  $\geq 2$  h in five (10%) patients, independently of



**Figure 1** Sleep–wake disturbances (%) 6 months<sup>2</sup> and 3 years after traumatic brain injury. Excessive daytime sleepiness: Epworth sleepiness scale  $\geq 10$ . Fatigue: Fatigue Severity Scale  $> 4.0$ . Post-traumatic hypersomnia: increased sleep need of at least 2 h compared with pre-TBI conditions. Insomnia: problems in falling asleep or sleeping through.

TBI characteristics. However, behaviourally induced insufficient sleep syndrome (chronic sleep deprivation) was not diagnosed in any patient, for none of these subjects suffered from EDS. Five patients (10%) met the diagnostic criteria for insomnia (6 months after TBI: 5%). All five insomnia patients were diagnosed as having depression, one with anxiety symptoms and three with fatigue.

### Fatigue

Twenty-six patients (51%) reported fatigue-associated symptoms including increased daytime tiredness, lack of energy and exhaustion since TBI. Fatigue as defined as  $FSS \geq 4.0$  was present in 18 patients (35%, mean FSS value:  $3.3 \pm 1.6$ ; 6 months after TBI: 17%). There were no associations between fatigue parameters and TBI severity, localisation or outcome, nor with sleep duration, age or gender. There was, however, a moderate correlation between FSS and depression symptoms as assessed with the BDI ( $r=0.46$ ,  $p=0.001$ ), and with anxiety symptoms (HADS;  $r=0.37$ ,  $p=0.007$ ). Six fatigued patients pathologically scored on depression scales.

### Excessive daytime sleepiness

Fifteen patients estimated their sleep latency at bedtime below 10 min. Epworth Sleepiness Scale scores (overall mean  $5.7 \pm 3.2$ ) were  $\geq 10$  in six patients (12%; 6 months after TBI: 28%). All six patients with EDS ( $ESS \geq 10$ ) classified this post-traumatic symptom as serious and disabling. Two of these patients were involved in car accidents because of sleep attacks. Another two patients (both with ESS values  $< 10$ ) reported having almost caused car accidents because of impaired vigilance. Comparing the presence of EDS at both time points (6 months and 3 years), the McNemar test did not reveal a significant improvement during this interval ( $p=0.21$ ). Automatic behaviour (ie, recurrent episodes of microsleep during which semipurposeful, non-sense activities are performed) was reported by three patients (two of them with ESS scores above 10). Furthermore, 25 patients (50%) performed diurnal naps during at least 2 days per week. EDS occurred irrespective of TBI severity or localisation, or psychiatric symptoms. Clinical outcome, as assessed with the GOS, however, was associated with subjective EDS ( $r=0.42$ ,  $p=0.04$ ). Four patients with EDS suffered from concomitant fatigue. None was diagnosed as having depression or anxiety disorder.

Post-traumatic narcolepsy with cataplexy, behaviourally induced insufficient sleep syndrome and restless legs syndrome were not diagnosed in any patient. Based on questionnaires and interviews, we suspected obstructive sleep apnoea syndrome in five patients (6 months after TBI: polysomnographic confirmation of obstructive sleep apnoea in seven patients). Three of these patients suffered from EDS or fatigue.

Altogether, we found sleep–wake disturbances in 34 (67%) of our TBI patients, and we could not identify other causes for SWD than the trauma itself in 23 (45%) TBI patients. Furthermore, we did not observe that differences in sleep–wake disturbances were linked to current medication or to the ability to work.

### DISCUSSION

Three years after TBI, sleep–wake disturbances remain a significant problem in a majority of patients: post-traumatic sleep–wake disturbances were diagnosed in 34 patients (67%), whereas 32 patients (63%) suffered from impaired vigilance (fatigue, EDS, post-traumatic hypersomnia), and five patients (10%) from insomnia. Psychiatric symptoms including depres-

sion and anxiety were found in six patients with impaired vigilance, and in all patients with insomnia. Three EDS patients reported symptoms alluding to obstructive sleep apnoea syndrome. In 23 patients (45%), we could not identify any other cause for SWD than the trauma itself.

Compared with 6 months after trauma, the prevalence of EDS (as assessed with the Epworth Sleepiness Scale) decreased (from 28% to 12%), but this improvement was not significant.<sup>2</sup> The mean ESS score decreased from 7.5 to 5.7. On the other hand, the portion of subjects suffering from fatigue (as assessed by the Fatigue Severity Scale) increased from 17% to 35%. Together with our observation that—at least in TBI patients—fatigue and EDS often coexist, thus, there might be a continuum of TBI-related fatigue and EDS. In other words, we assume that in the course after TBI, sleep propensity during daytime fades, but a rather unspecific tiredness persists and may become more prominent. Lastly, the prevalence of post-traumatic hypersomnia increased slightly to 27%, indicating that sleep need after TBI remains pathologically increased for a long period of time.

The pathophysiological basis of post-traumatic sleep–wake disturbances is not known. In a recent pilot study, we found a significant decrease of neurons producing the wake-promoting neurotransmitter hypocretin (orexin) in the hypothalamus of deceased TBI patients, when compared with controls.<sup>15</sup> This loss and other structural changes in sleep–wake regulations neuronal systems might contribute to sleep–wake disturbances after TBI, together with physical and psychiatric comorbidities.

In this study, therefore, we also assessed the influence of psychiatric symptoms on post-traumatic SWD. We found an association between fatigue and both depression and anxiety symptoms. However, only six TBI patients with fatigue were diagnosed as having depression. In the other 12 fatigued patients, depression scores were normal. The association between depression and SWD was strongest in insomnia: all insomnia patients were diagnosed as having depression. EDS and hypersomnia, on the other hand, were not associated with psychiatric symptoms. These results suggest that psychiatric complications of TBI are not major causal factors for the occurrence of disturbed sleep and wakefulness following trauma. Besides psychiatric symptoms, we could not identify risk factors such as TBI severity or localisation for post-traumatic SWD.

This study has limitations. First, we applied only subjective measures for the present follow-up study, but we did not repeat sleep laboratory tests in our patients. Second, we lost 14 patients (22%) to follow-up. Third, this study cohort does not represent the complete TBI population: to study post-traumatic sleep–wake disturbances, we included only patients without pre-morbid conditions, but many trauma patients suffer from comorbid psychiatric or neurological disorders, which are risk factors for TBI.

In summary, this is the first long-term study of post-traumatic sleep–wake disturbances in a well-described TBI population with multiple time points of examinations. In the light of our observation that impaired vigilance and increased sleep need persist for many years after TBI, future research needs to address systematically the aetiology of post-traumatic SWD, which will give way to better and tailored treatments.

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**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** Ethics approval was provided by the Ethical Committee, University of Zurich.

## Research paper

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